Yale Liver Center

2023 LIVER CENTER RETREAT

The Yale Liver Center held its annual retreat at the Water's Edge Resort and Spa, in Westbrook, Conn., on September 10, 2023.

Topics discussed at the event included important resources for Yale Liver Center members including the new academic unit Biomedical Informatics and Data Science and the Yale Center for Clinical Investigation, cutting-edge liver research at Yale in metabolism and in immunobiology, and the projects undertaken by junior faculty and postdoctoral fellows through the center's pilot grant program and institutional liver training grant.

There were over 100 registrants and 30 poster presentations at the event, according to Michael H. Nathanson, MD, PhD, director of the Yale Liver Center and Gladys Crofoot Professor of Medicine (Digestive Diseases) and professor of cell biology, who added that on-site daycare was provided to maximize the ability of individuals to attend the retreat.

A new feature of the event this year was a session that focused on the accomplishments of disease-aligned research teams, said Mario Strazzabosco, MD, PhD, professor of medicine (digestive diseases), co-director of the Yale Liver Center, and organizer of the retreat. "These 10 teams exploit new discoveries and innovations to advance the care of patients with complex liver conditions and sustain destination programs able to provide highly differentiated world class care," he said. "What was evident was the richness of the research, the large number of patients treated, and the ability to cover many of the unmet needs of patients with liver disease—the tripartite mission of an academic medical center and school realized at his best."

Strazzabosco noted the participation of members from a variety of departments, both clinical and basic, which illustrates the interdisciplinary breadth of liver research at Yale.

The retreat helped raise awareness about recent scientific advances that resulted from Liver Center initiatives, said Guadalupe Garcia-Tsao, MD, FRCP, professor of medicine (digestive diseases), who led a session on Liver Center core offerings. "It also made participants more aware of what everybody else is doing within the Liver Center and—perhaps more importantly—outside of the Liver Center," she said.

The occasion is a forum for people with different interests and backgrounds to share ideas and information, added Catherine Mezzacappa, MD, MPH, clinical fellow in the Section of Digestive Diseases, who presented at the event. "For example, I'm interested in the interactions between metabolism and serious liver diseases, and I learned a great deal from Gerald Shulman, MD, PhD, who spoke about peripheral insulin resistance and how this can be modified," she said. "This kind of sharing across disciplines generates new questions and opportunities."

Nathanson hopes the retreat allowed participants to network with colleagues and improve their understanding of current resources at Yale to support their research. "The annual event is a wonderful opportunity to further enhance the already extensive degree of collaborations among our membership and beyond," he said.

A main highlight of the event was the keynote lecture given by Nancy J. Brown, MD, Jean and David W. Wallace Dean of the Yale School of Medicine and C.N.H. Long Professor of Internal Medicine, who spoke about strategic planning for discovery and the ways Liver Center members can participate in many new initiatives at the school level.

This article was written by Serena Crawford

2022-2023 LIVER CENTER PILOT PROJECTS

The morning session began with presentations from the recipients of our 2022-2023 Pilot Project Awards. The Pilot Feasibility Program seeks to introduce new investigators and ideas to the Center, to promote novel ideas that may advance the field of hepatology, and to enable investigators to obtain data for future grant submissions. This program has enabled the Center to continually revitalize its membership and to capitalize on new technologies and research opportunities of importance to the continued development of the Center's research base. For example, the program has enabled us to bring new investigators into the Center with expertise in diverse but cutting-edge areas. Pilot Feasibility projects also were pivotal for the development of novel technologies such as iPSC-derived cholangiocytes, as well as biliary organoids derived from liver tissue or bile.

Vikas Gupta, MD, PhD
Assistant Professor of Medicine
Digestive Diseases

Project Title: *Role of Cholangiocyte Derived Wnts During Cholestatic Injury*

This pilot proposal will utilize murine biliary injury models, genetics, and sequencing to discover how changes in the expression of cholangiocyte derived Wnts affects the cellular phenotype of adjacent mesenchyme during biliary injury in the large ducts using cell type specific gain and loss of function.

Xiaoyong Yang, PhD
Professor
Comparative Medicine

Project Title: *Characterizing novel paracrine factors in chronic liver disease*

The intercellular crosstalk between the parenchymal cell of the liver, the hepatocyte, and other cell types such as immune cells, stellate cells, and endothelial cells, is much undiscovered. Our long-term goal is to examine paracrine factors that mediate cell-cell communication in disease progression from NASH, fibrosis to HCC. The objective of this pilot proposal is to characterize the role of the hepatocyte-derived paracrine factor TFF2 in intercellular signaling during liver fibrogenesis.

Won Jae Huh, PhD
Assistant Professor
Pathology

Project Title: *Sex-Hormone-Induced Differential Expression of EGF Receptor (EGFR) in Hepatocytes and Its Implication for Hepatic Steatosis*

The main hypothesis of this study is that testosterone regulated hepatic EGFR expression is an underlying mechanism of sex disparity in NAFLD. We will utilize mouse models and hepatocyte organoids to dissect the mechanism how testosterone regulate EGFR and how EGFR signaling regulates lipid metabolism and accumulation in hepatocytes.

Jason Bini, PhD
Associate Research Scientist
Radiology & Biomedical Imaging

Project Title: *Positron Emission Tomography imaging of 11β-hydroxysteroid dehydrogenase type 1 in NAFLD*

This pilot project will allow examination of 11β-HSD1 whole-body distribution levels in human individuals with non-alcoholic steatohepatitis (NASH) using the [18F]FMOZAT PET radioligand. The results of this study will be important to understand the metabolic changes associated with steatotic liver disease.

HEPATOLOGY T32 TRAINEES

The second session began with presentations from the current Hepatology T32 trainees. This NIDDK-sponsored training program has been continuously supported for the past 44 years. The goal of this training program is to provide basic laboratory, translational, or clinical research training for physicians who have completed clinical training in gastroenterology in preparation for careers as independent investigators in academic hepatology and to provide research training for recent PhD graduates to prepare them for careers as independent investigators in basic liver-related research.

Jeremy Puthumana, MD
Clinical Fellow | Digestive Diseases

Project Title: *Biomarkers for the Diagnosis and Prognosis of AKI in Patients with Cirrhosis*
Primary Mentor: Pramod Mistry
Faculty Committee: Pramod Mistry, Chirag Parikh, Dennis Moledina, and Michael Nathanson

Xing Feng, PhD
Postdoctoral Fellow | Immunobiology

Project Title: *Role of Gpr56 and Gpr97 signaling in fetal liver hematopoiesis*
Primary Mentors: Joao Pereira & Silvia Vilarinho
Faculty Committee: Yasuko Iwakiri, Silvia Vilarinho, and Joao Pereira

Catherine Mezzacappa, MD, MPH
Clinical Fellow | Digestive Diseases

Project Title: *Investigating gene-environment interactions in steatotic liver disease and HIV*
Mentors: Tamar Taddei & Amy Justice
Faculty Committee: Tamar Taddei, Amy Justice, Xiaomei Ma, Rachel Perry, Michael Nathanson, Chen Liu

Jonathan Pascale, PhD
Postdoctoral Fellow | Pharmacology

Project Title: *Characterization of a novel knockin mouse to assess MKP5 druggability in tissue fibrosis*
Primary Mentor: Anton Bennett
Faculty Committee: Anton Bennett, Elias Lolis, Barbara Ehrlich, Naftali Kaminski

The retreat also featured three invited talks which highlighted some of the developments in the School of Medicine that may be relevant to our Liver Center members.

CLINICAL RESEARCH

David Coleman, MD
Interim Director, YCCI
Emeritus Professor, Yale School of Medicine

How YCCI can help Clinical Research in Hepatology

BIOINFORMATICS & DATA SCIENCE FOR THE STUDY OF LIVER DISEASE

Hua Xu, PhD
Robert T. McCluskey Professor of Biomedical Informatics and Data Science
Vice Chair for Research and Development
Assistant Dean for Biomedical Informatics

Biomedical Informatics and Data Science for Clinical And Translational Research at Yale

LIVER VASCULAR BIOLOGY

Silvia Vilarinho, MD, PhD
Associate Professor of Medicine
Digestive Diseases and of Pathology
Associate Director, Yale MD-PhD Program
Director, Internal Medicine Physician Scientist Training Program

Liver Endothelial Cell Biology

LIVER CENTER THEMES

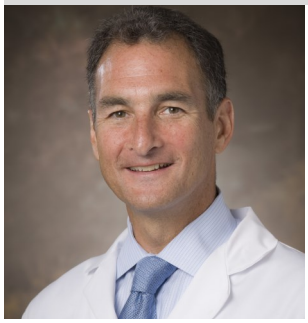
Three invited speakers updated the membership on the latest developments in each of the three main themes of the Liver Center as shown below.

Theme 1: Immunobiology & Inflammation

Andres Hidalgo, PhD
Professor of Medicine (Immunobiology)

Neutrophils: new paradigms

Theme 2: Hepatic Metabolism



Gerald I. Shulman, MD, PhD
George R. Cowgill Professor of Medicine (Endocrinology)
Professor of Cellular & Molecular Physiology
Co-Director, Yale Diabetes Research Center

Targeting hepatic mitochondrial fat oxidation to treat MASLD, MASH, hepatocellular cancer and cardiometabolic disease

Theme 3: Epithelial Biology & Pathobiology

Romina Fiorotto, PhD
Assistant Professor of Medicine (Digestive Diseases)
Associate Director, Cellular & Molecular Physiology Core

Novel and Multi-Omics approaches for cholestatic liver diseases and beyond

AVAILABLE CENTER CORE SERVICES

Another portion of the retreat was a roundtable chaired by Dr. Garcia-Tsao. Each of the Core Directors and Associate Directors discussed with the members the offerings of each core and potential new technologies needed by the members. Also during this session, a questionnaire was distributed among the members to better understand their evolving needs. Below is a list of current available core services.

ADMINISTRATIVE

PILOT FEASIBILITY PROGRAM
Pilot grants given annually to promote studies of liver disease

ENRICHMENT PROGRAM
Monthly seminar series, annual Klatskin/Boyer Lectureship, annual Center retreat, extended visiting professorship, research in progress series

MORPHOLOGY

CONFOCAL, SUPER-RESOLUTION, MULTIPHOTON IMAGING
Leica SP5 Confocal Microscope
Stellaris 8 DIVE Multiphoton Microscope
Zeiss LSM 880 Airyscan Confocal Microscope
Leica SP8 Gated STED 3X Super Resolution
Bruker Opterra II Swept Field Microscope
Bruker Luxendo Light Sheet Microscope
Bruker Vutara 352 Super Resolution Microscope

ELECTRON MICROSCOPY
Tecnai 12. biotwinFEI Tecnai TF20 FEG

OTHER MICROSCOPY TOOLS
Zeiss Axio Observer epifluorescence microscope
Olympus BX51 multi-headed brightfield microscope
Dissecting microscope
Zeiss Discovery 8 SteReo

IMAGE ANALYSIS WORKSTATIONS
4 PC workstations dedicated to image analysis. Software from Zeiss (ZEN blue), Leica (LAS X), Bitplane (Imaris), SVI (Huygens Deconvolution) and Perkin Elmer (Volocity) are available to users.

CELLULAR-MOLECULAR

ISOLATED CELL PREPARATIONS
Hepatocytes, cholangiocytes, endothelial cells, stellate cells, portal fibroblasts and hepatic lymphocytes, primarily from mice and rats. Human hepatocytes when available.

PROTEIN & GENE EXPRESSION
Quantitative real time PCR and infrared imaging detection . Altering gene expression in these cells using siRNA transfection and adenovirus infection technologies

IPSC/LIVER ORGANOID
On request, PBMCs are transferred to the Yale Stem Cell Center (YSCC) for reprogramming into iPSC. YSCC will generate at least 3 clones of iPSCs for each PBMC sample. iPSCs can be differentiated into liver cells (biliary cells or hepatocytes) and made available. Liver organoids available upon request.

CELL CULTURE FACILITIES
Available for short– and long– term cultures and cell lines.

CLINICAL-TRANSLATIONAL

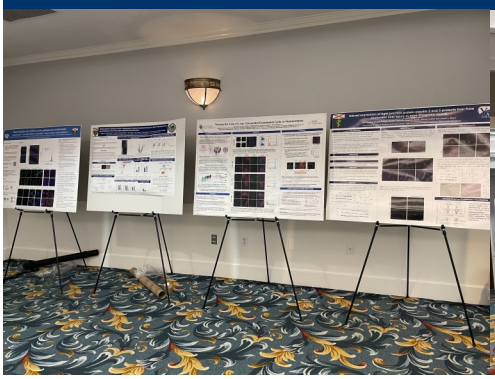
BIOSTATISTICAL SUPPORT
Two biostatisticians available for expertise in the design, conduct, and analysis of patient-oriented studies, as well as methodological development, education, and training

BIOINFORMATICS SUPPORT
Bioinformatics analysis support for Liver Center members through the Yale Center for Genome Analysis (YCGA) bioinformatics core.

RESEARCH COORDINATOR
Recruitment of patients and collection of blood samples and other biospecimens

PATIENT REGISTRY
Patient databases on diagnoses including: chronic hepatitis C, cirrhosis, chronic hepatitis B, PBC, autoimmune hepatitis, PSC, hepatocellular carcinoma, NAFLD, and cholangiocarcinoma

POSTER SESSION



NEW! CHILDCARE @ RETREAT

This year, an exciting new addition to our event was that we were able to offer childcare for anyone who attended the retreat. We would like to thank the staff from the Medical Schools Bodel Childcare Center for spending the day with us and taking great care of the kids!

FEATURED PUBLICATIONS FROM LIVER CENTER MEMBERS
FURTHER HIGHLIGHT THE BREATH OF SCIENTIFIC AND TECHNICAL INNOVATION

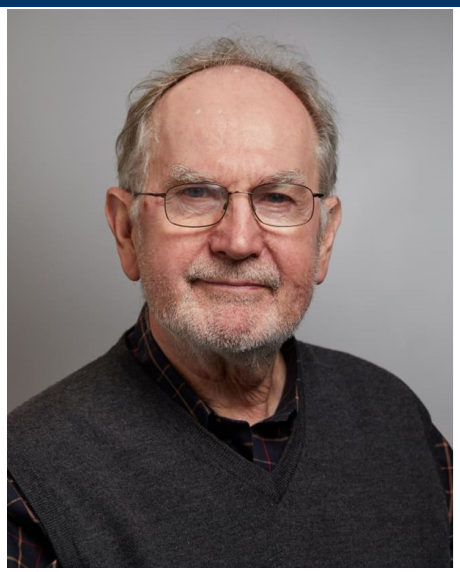
Dean Yimlamai, MD, PhD
Assistant Professor of Pediatrics & Experimental Pathology
Director of Pediatric Hepatology Research

Hepatocyte CYR61 polarizes profibrotic macrophages to orchestrate NASH fibrosis

Mooring M, Yeung GA, Luukkonen P, Liu S, Akbar MW, Zhang GJ, Balogun O, Yu X, Mo R, Nejak-Bowen K, Poyurovsky MV, Booth CJ, Konnikova L, Shulman GI, Yimlamai D.
Science Translational Medicine. 2023;15(715):eade3157. PMID: 37756381

Nonalcoholic steatohepatitis is a severe form of liver disease that has no cure and whose etiology is incompletely understood. Mooring et al. show that the protein cysteine-rich angiogenic inducer 61 (CYR61) promotes liver-infiltrating macrophage polarization in NASH, leading to inflammation and fibrosis via NF-κB–linked and PDGFa/b-linked signaling pathways, respectively. The authors also developed a CYR61-blocking antibody that ameliorated inflammatory and profibrotic gene expression in macrophages in vitro and reduced fibrotic collagen deposition in a NASH model in vivo, demonstrating proof-of-principle targeting of this signaling axis.

FEATURED PUBLICATION



Richard A. Flavell, PhD
Sterling Professor of Immunobiology

Wajahat Z. Mehal, MD
Professor of Medicine (Digestive Diseases)

Eleanna Kaffe, PhD
Associate Research Scientist (Immunobiology)

Humanized mouse liver reveals endothelial control of essential hepatic metabolic functions

Kaffe E, Roulis M, Zhao J, Qu R, Sefik E, Mirza H, Zhou J, Zheng Y, Charkoftaki G, Vasiliou V, Vatner DF, Mehal WZ; AlcHepNet; Yuval Kluger, Flavell RA.

Cell. 2023; 186(18):3793-3809.e26. PMID: 37562401

A comprehensive human liver tissue was established in a mouse host that consists of all human-relevant parenchymal and non-parenchymal cell types and mimics the cellular composition, histological architecture, and functional properties of a human liver. This highly human-relevant murine model allows investigation of human-specific metabolic features and liver cell type interactions. Using this model, it was found that essential hepatocyte functions like cholesterol uptake and bile acid conjugation are not cell autonomous but are highly dependent on signals from the adjacent endothelial cells. This model can develop human fibrosis upon damaging insult in liver epithelial cells and NAFLD upon western diet feeding. This model can be used to study mechanisms driving human liver fibrosis and human NAFLD and their consequences on human specific liver functions.

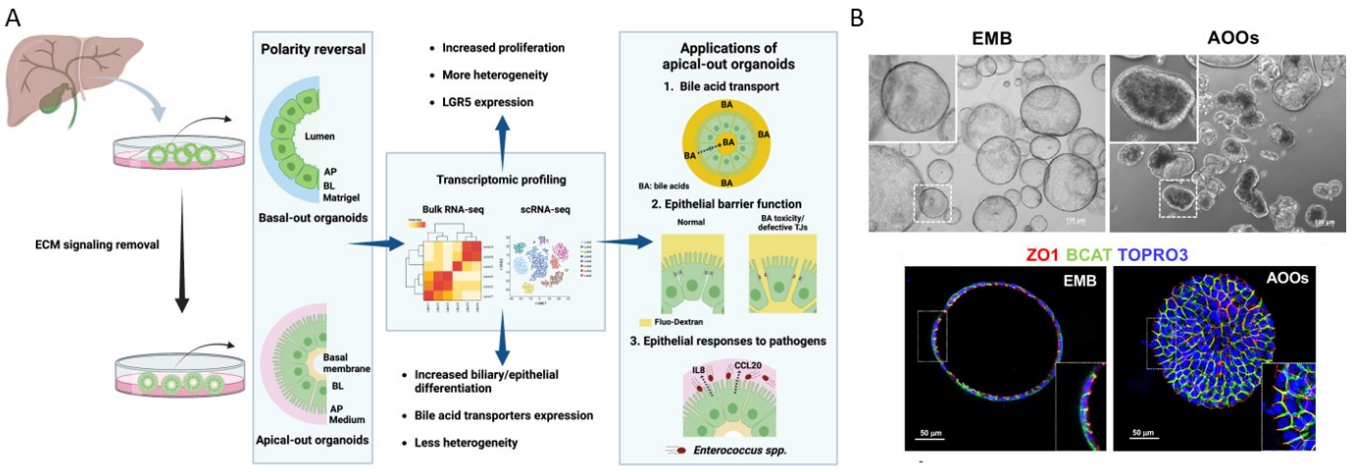
FEATURED PUBLICATION

Romina Fiorotto, PhD
Assistant Professor of Medicine
Digestive Diseases

Cell-matrix interactions control biliary organoid polarity, architecture, and differentiation.

Fiorotto R, Mariotti V, Taleb SA, Zehra SA, Nguyen M, Amenduni M, Strazzabosco M.
Hepatology Communications. 2023; 7(4):e0094. PMID: 36972396

Human biliary organoids are an attractive technology to study the pathobiology of biliary diseases, but current models are limited by the inaccessibility of their apical pole and the presence of extracellular matrix (ECM). This study published in Hepatology Communications, describes a new approach that overcomes these limitations by generating liver derived 3D human biliary organoids, in which the cell polarity is inverted, and the apical membrane is easily accessible. This approach is based on the modulation of b1-integrin signaling, that controls the apical-basal orientation. Apical-out organoids generated in this study exhibit less cellular heterogeneity and improved functional maturation of cells and reproduce essential functions of the biliary epithelium such as bile acid transport and epithelial barrier function. Moreover, the exposure of apical -out biliary organoids to different pathogenic bacterial strains elicit specific innate immune responses making them ideal to study epithelial pathogen interactions. This novel approach represents a powerful new model to study liver biology and especially cholangiocyte biology, cell-cell and cell-ECM interactions, epithelial-pathogen interactions, and the pathobiology of various cholangiopathies.



(A)The cartoon illustrates the experimental design and the main findings of the study. (B)Brightfield and confocal images showing respectively the change of morphology in apical-out organoids (AOOs) and the distribution of markers of cell polarization (ZO-1, tight-junctions marker; b-catenin, basolateral membrane)